ISSN 2660-972X

Current Bioscience. 2021;1(1):e04
DOI: https://doi.org/10.51959/cb.2021.v1n1.e04

REVIEW *in* BACTERIOLOGY

Gene expression in *Staphylococcus aureus* skin infection

Marco Palma *^

* Independent researcher, Torrevieja, Spain

^ Corresponding author:
Marco Palma, phd@marcopalma.es

Gene expression in *Staphylococcus aureus* changes during infection to survive its host. Therefore, to find new strategies to combat staphylococcal infections, it is important to understand the mechanisms that this pathogen uses to adapt to its host and how the host responds to the presence of staphylococcal cells. It has been reviewed two studies of gene expression in *Staphylococcus aureus* during skin infections, one study using a rabbit skin infection model and the other study using a diabetic skin infection model in mice. It was compared the two gene expression profiles to find similarities and differences. Many genes did not show any differences in gene expression in *S. aureus* during the skin infection compared to the control groups. However,19 genes were upregulated in both systems include chaperones (e.g., *groES*, *groEL*, *grpE*, *dnaK9*), *sodM*, *hrcA*, *sbi*, and the gene encoding a cadmium-exporting ATPase protein. Also, four genes were downregulated in both systems including a gene that encodes a hydrolase and three genes for hypothetical proteins. Also, there was a group of genes expressed in different ways in the two systems. The gene expression of *sarU*, transcriptional regulators of the LysR family, Cro family, crp family, TetR family, tenA, and many hypothetical proteins were upregulated in the rabbit system but downregulated in the mouse system. The genes *rps*, *rpl*, *rpm*, and several others involved, for example, in translation and transcription were downregulated in the rabbit system but upregulated in the mouse system. Many genes that showed significant changes in overall gene expression in the rabbit model were unaffected in the mouse model. For example, in the rabbit skin infection model increased important gene regulators like *agr* and *sarV*, while some stress-response genes (e.g., *sigB* and *lexA*) were downregulated. The gene expression of several staphylococcal genes encoding virulence factors such as fibronectin-binding proteins, hemolysins, coagulases, complement inhibitory proteins, Emp, and many exotoxins were upregulated while clumping factor A was downregulated. Besides, some genes showed expression changes in the mouse model, but not in the rabbit model. For example, *sarA*, *rot*, *ecb*, *ctsR*, *spx*, many ribosomal proteins, and hypothetical proteins increased, while *cap5k*, *lysE*, *rusA*, and many hypothetical proteins decreased in the mouse model but they were unaffected in the rabbit model. On the other hand, the host responded to the *S. aureus* infection by inducing the expression of genes encoding host inflammatory cytokines, receptors, genes associated with neutrophil adhesion and migration, inflammation, and immune cell trafficking. In conclusion, the level of gene expression changed both in the pathogen and the host during the skin infection. The information of gene expression can make significant contributions to understand which genes are involved in the infection process, which can be targeted for antimicrobial chemotherapy.

Keywords: gene expression, staphylococcus aureus, skin infection, gene regulation, animal model, host.

ISSN 2660-972X
Current Bioscience. 2021;1(1):e04
DOI: https://doi.org/10.51959/cb.2021.v1n1.e04

Introduction

The success of a microbe to colonize its corresponding host depends on several factors, including the ability of the microbe to control the expression of its genes during the colonization of its host and on the signaling events initiated by the colonized host in response to the infecting microorganism. The initial signaling events are crucial to activate rapidly the host defense mechanisms, which results in the clearance of the pathogen, limiting its further spread beyond the site of infection. Transcriptional analysis of a microorganism and its corresponding host can be combined in such a way that can provide a truly comprehensive picture of the gene expression patterns induced in the microbe when it encounters the host and on the signaling pathways induced in the colonized host by the infecting bacteria. This can be done in a single experiment using the technology of DNA microarrays.

Staphylococcus aureus is an important nosocomial and community-acquired pathogen. It commonly causes local and systemic infections in mammals ranging from minor wound infections to life-threatening conditions such as endocarditis, osteomyelitis, and toxic shock syndrome (1). *S. aureus* responds to the host environment by altering its gene expression (2). However, the entire stimuli to which *S. aureus* responds to the host cells or to host factors remained undetermined. Several investigations have shown that the contact of a microbe with eukaryotic host cells results in the expression of genes that are specifically required for survival or virulence (3,4).

The lack of alternative therapies to antibiotics against *S. aureus* is a major problem in the treatment of staphylococcal disease, especially due to the increase in methicillin-resistant strains (MRSA). After the introduction of methicillin in the 1960s (5), the incidence of MRSA has grown significantly (6,7). The most likely explanation for this appearance and spread of MRSA is the increased and indiscriminate use of broad-spectrum antibiotics. The increasing prevalence of multidrug-resistant strains and the recent appearance of strains with reduced susceptibility to vancomycin (8), the antibiotic of last resort, raise the specter of untreatable staphylococcal infections and add urgency to the search for new anti-infective strategies. To find new strategies is important to understand the mechanisms that *S. aureus* uses to adapt to its host and how the host responds to the presence of staphylococcal cells. Therefore, we want to review and compare the expression profiles of the two infection models and identify important genes.

Method

It was conducted an extensive literature search using validated keyword filters to select articles related to *Staphylococcus aureus* gene expression in vivo or animal models. The research was conducted on articles published from 1 January 2000 to 31 January 2021, and an in-depth and selective search was performed on biomedical bibliographic databases PubMed, SCOPUS, and Google Scholar. Finally, the studies that contained tables with changes in *S. aureus* transcriptome during the infection were chosen. The tables with the fold-change expression were compared using Microsoft access.

Results

Selected studies

Mainly two studies fit the criteria described above. Malachowa et al. (2015) monitored gene expression changes in *S. aureus* transcriptome and host during abscess formation in a rabbit skin infection model (9). Jacquet et al. (2019) investigated how the diabetic environment affects the *S. aureus* gene expression in diabetic models of *S. aureus* skin infection in mice (10).

Technical differences between the two skin infection models

The hyperglycemic mice were generated through daily injections over five days with 50 mg/kg of body weight of streptozotocin. In both studies, the animals were infected with 106-8 CFUs of *S. aureus* strain USA300 subcutaneously. In the rabbit study, bacterial RNA isolated from the abscess 24 hours post-infection was analyzed on Affymetrix GeneChip. cDNA synthesized from total RNA from days one to 14 post-infection was analyzed using RT2 Profiler PCR Array Rabbit Inflammatory Cytokines and Receptors platform (11). In the mice study, it was used a dual transcriptome sequencing (RNAseq) approach to analyze the mRNA level differences between control and diabetic mice one day after infection.

General overview of gene expression in both systems

The expression of 1262 genes was unaffected in either animal model. Within the first 24 h, significant changes in gene expression were detected for *S. aureus* genes involved in basic functions and survival. 731 genes were upregulated and 423 genes downregulated only in the rabbit model while 84 genes were upregulated and 27 downregulated only in the mouse model. 19 genes were upregulated and

four genes were downregulated in both systems. 34 genes that were upregulated in the rabbit were downregulated in mice while 20 genes that were downregulated in the rabbit were upregulated in mice.

Genes upregulated and downregulated in both system

The 19 genes upregulated in both systems include chaperones (e.g., *groES*, *groEL*, *grpE*, *dnaK9*), *sodM*, *hrcA*, *sbi*, and the gene encoding a cadmium-exporting ATPase protein. Also, four genes were downregulated in both systems including a gene that encodes a hydrolase and three genes for hypothetical proteins

Genes upregulated and downregulated only in the rabbit skin infection model

The functional class most frequently represented among these genes were those involved in transport and metabolism of amino acids (e.g., *hutH*, *arcB-D*, etc.), nucleotides (e.g., *purA*, *deoD*, *tmk*, etc.), inorganic ions (e.g., *sirA-C*, *phnB*, *phnC*, *phnE*, etc.), carbohydrate (e.g., *bglA*, *fruA*, *fruB*, etc.).

The transcripts of the accessory gene regulator agr system (*agrA*, *agrB*, and *agrC*) were downregulated (8- to 19-fold) while sarV, a member of the SarA protein family, increased 6.4-fold. The gene expression of the genes of the Sigma B operon (*sigB*, *rsbW*, and *rsbV*) that have been shown to respond to environmental stresses decreased 2- to 4-fold. Also, the gene expression of two different genes encoding TetR family transcription regulators was upregulated. TetRs are widely associated with antibiotic resistance and the regulation of genes encoding small-molecule exporters (12). Two genes encoding MarR family transcription regulators were upregulated 10.4-fold while the other was downregulated 2.46-fold. The members of the MarR family of transcription factors are critical for bacterial cells to respond to chemical signals and to convert such signals into changes in gene activity (13). The MsrR transcriptional regulator which affects resistance to methicillin and teicoplanin was upregulated by 2.3-fold. LexA repressor that regulated the expression of the SOS gene was downregulated by 3.4-fold. The *srrA* genes of the two-component regulatory system (TCRS) positively influence the transcription of genes involved in aerobic respiration in response to changes in respiratory flux were downregulated by 3-fold.

The gene expression of several *S. aureus* genes encoding virulence factors changed during the first 24 hours of skin infection. The expression of *fnbA* increased by 2.3-fold as well as the gene encoding fibronectin-binding proteins (e.g., *fnbA*, *fnbB*, *sdrC*, *sdrD*, *sdrE*, SAUSA300_1028, and SAUSA300_1029) that showed substantially increased mRNA levels (2- to 125-fold). The *sarA* locus up-regulates the expression of many cell wall proteins including *FnbA*. Fibronectin-binding proteins contribute to the colonization and infection of the host by *S. aureus* via adhesion to fibronectin present in the extracellular matrix of the tissues. They play a role in the virulence of *S. aureus* skin abscess infection, infective endocarditis, bacteremia, sepsis, pneumonia, and foreign body infections (14).

The gene expression of spa that had been described previously as down-regulated by *sarA* locus (15), increased in the skin abscess by 4.0-fold. Protein A effectively blocks the formation of IgG hexamers and subsequent complement activation (16). The gene expression of *clfA*, a cell surface-associated protein that binds fibrinogen promoting *S. aureus* colonization of host tissues and biomedical devices under physical stress (17), was downregulated by 6.5-fold. The gene expression of hemolysin gamma A gene (*hlgA*, SAUSA300_2365) that have been described previously to require both Sae and Agr (18), in this model increased 20.8-fold. Actually, *hlgB* (SAUSA300_2367) and *hlgC* (SAUSA300_2366) increased by 76.3- and 27.4-fold, respectively. Haemolysin gamma A, B, and C (HlgABC) displayed cytotoxicity to monocytes and natural killer cells (19).

The expression of genes encoding coagulase (Coa), and two von Willebrand factor binding proteins (vWbp) with coagulase activity that are required for septicemia and abscess formation (20) increased 12- to 34-fold. Coa is involved in the virulence of *S. aureus*. The fibrinogen-binding motifs also found in coagulase block neutrophil αMβ2 adherence to fibrinogen and attract fibrinogen to the bacterial surface, forming capsule-like structures that block phagocytosis (21).

The gene expression of a gene (scin) belonging to the family of *S. aureus* complement inhibitory proteins increased more than 57-fold. They share a common domain of three helices at the C3 binding region (22) and are implicated in the *S. aureus* evasion of the complement-mediated immune response. Surprising the gene efb which encodes another complement inhibitory protein was unaffected. Also, gene expression of emp that encodes a protein with a fibrous structure that binds to different extracellular matrices proteins increased 11.7-fold (23). Emp plays an important role in low-iron-induced biofilm formation (24). The expression of the gene *sasC* encoding the *S. aureus* surface protein C which is involved in cell aggregation and biofilm accumulation (25) increased by 10-fold. The gene expression of gene encoding SpoVG which

ISSN 2660-972X
Current Bioscience. 2021;1(1):e04
DOI: https://doi.org/10.51959/cb.2021.v1n1.e04

is a repressor of the expression of *sasC*, decreased by 8.3-fold.

The gene expression of genes encoding exotoxins increased. For example, the mRNA level of genes (SAUSA300_0396, _0397,_0399, _0400, _0401,_0402, _0404, _00407 and SAUSA300_1059 to _1061) encoding staphylococcal superantigen-like (SSL) proteins increased from 5.0- to 125-fold. SSL proteins have been shown to help *S. aureus* to escape from the protective adaptive immune response of the host and thus may contribute to bacterial pathogenicity (26,27). The gene expression of several multidrug resistance genes was upregulated like *fmtB* methicillin resistance proteins (SAUSA300_2109 and SAUSA300_2110) that increase by 42.5- to 38.2-fold, multidrug resistance protein B (SAUSA300_2298) that increased by 12.2-fold, and multidrug resistance protein A defense mechanisms/virulence (SAUSA300_2299) that increased 37.0-fold.

Genes upregulated and downregulated only in the mouse skin infection model

The accessory regulators *sarA*, *rot*, *ecb*, *ctsR*, *spx*, many ribosomal proteins, and hypothetical proteins increased while *cap5k*, *lysE*, *rusA*, and many hypothetical proteins decreased only in the mice model and not in the rabbit model.

Genes with an opposite expression between the two systems

The gene expression of *sarU*, transcriptional regulators of the LysR family, Cro family, *crp* family, TetR family, *tenA*, and many hypothetical proteins were upregulated in the rabbit system but downregulated in the mouse system. The genes *rps*, *rpl*, *rpm*, and several others involved, for example, in translation and transcription were downregulated in the rabbit system but upregulated in the mouse system.

Gene expression in the host

In the rabbit, gene expression changes of 84 genes encoding host inflammatory cytokines and receptors were analyzed using PCR arrays. 11 genes were downregulated and 52 genes were upregulated 24 h post-infection compared to untreated healthy rabbits. The expression level of many transcripts encoding proinflammatory molecules was highly up-regulated such as IL8, IL1B, oncostatin M, CCR1, CXCR1, CXCR2, CCL4, and CCL3. The expression level of some proinflammatory molecules (e.g., CCR5, CXCR4, IL1A, IL1R1, IL8, and TNF) peaked on days three to six post-infection. Moreover, there is a group of molecules, including LTA, LTB, IL21, IFNAR2, CXCR3, IL17F, and CD40LG, whose expression increased throughout staphylococcal skin infection.

In the diabetic mice model, 231 genes were differentially expressed compared to the control group, of which 110 were upregulated while 125 were downregulated. Whatever the diabetic condition of infected mice, it increased the expression of genes encoding proteins involved in the adhesion of neutrophils, neutrophil migration, inflammation, and immune cell trafficking. Also, the genes with the major changes were those encoding Rho, Sarcospan, filamin A, IL-10, and genes associated with macrophages, fibroblasts, and endothelial cells. On the other hand, the genes associated with lipid, vitamin, and mineral metabolism, dermatological disease, and skeletal and muscular system development, EIF2 signaling, stearate signaling, and heme biosynthesis were downregulated.

Discussion

The global analysis of gene expression patterns makes it possible to identify genes that could be relevant for pathogenesis and the colonization of host tissues. *S. aureus* encounters hostile conditions in the host, in response to which it is believed that this organism alters its gene expression to allow adaptation and colonization of the host tissue. It has been reviewed two important in vivo studies that described gene expression of *S. aureus* and the host during skin infection based on two different animal models. The main differences between these two systems are that they are two types of animals and the levels of sugar or glucose in the blood of these animals. Such a level of sugar probably made some differences in gene expression between the two systems. Patients with diabetes may be more sensitive to *S. aureus* bacteremia due to tissue hyperglycemia, reduced oxygenation, and usually reduced immunity (28). *S. aureus* is the most frequently isolated pathogen in diabetic wound infections.

Many genes did not show any differences in gene expression in *S. aureus* in skin infection in rabbits, diabetic mice, and control groups. However, few genes were affected in the same way in both systems including chaperones (e.g., *groES*, *groEL*, *grpE*, *dnaK9*, *sodM*, *hrcA*, and *sbi*). Besides, there were genes expressed in different ways in the two systems (e.g., *sarU*, *lysR* family, *cro* family, *crp*, *tetR* family, *tenA*, *rps*, *rpl*, *rpm*, genes for hypothetical proteins, involved translation and transcription). Some genes are expressed only in one of the two systems which expression was unaffected in the other system. For example, in the rabbit skin infection model increased important gene regulators, including *agr* and *sarV*, while others were downregulated such as stress response genes

(e.g., *sigB* and *lexA*). The gene expression of several *S. aureus* genes encoding virulence factors such fibronectin-binding proteins, hemolysins, coagulases, complement inhibitory proteins, Emp, and many exotoxins were upregulated while clumping factor A was downregulated. Few genes were upregulated only in the mouse model including *sarA*, *rot*, *ecb*, *ctsR*, *spx*, many ribosomal proteins, and hypothetical proteins increased while *cap5k*, *lysE*, *rusA*, and many hypothetical proteins decreased.

The identification and characterization of genes encoding proteins implicated in bacterial pathogenesis may lead to new therapeutic drugs to treat staphylococcal infections (29). Early detection of infecting bacteria by the host is crucial for effective mobilization of innate and specific defense mechanisms. Several studies have described changes in host transcription during infection with a pathogen (30–33). In the skin infection models, the immune system of the rabbit response in the early stage of the infection by inducing the expression of genes encoding pro-inflammatory cytokines while in a later stage of the infection was induced the expression of receptors. The immune response of the diabetic mice induced the expression of genes associated with neutrophil adhesion and migration, infection, inflammation, and immune cell trafficking.

The staphylococcal genes with unclear function in infection can be mutated, and the constructed mutants can be subsequently characterized and their roles in pathogenesis determined. In this way, we can identify critical host responses during *S. aureus* infection. This information can make significant contributions in the field of *S. aureus* since many steps involved in the infection process can be targeted for antimicrobial chemotherapy, including adherence, invasion, and host defense evasion.

Declarations

Ethical approval
Not required.

Author contributions
M.P. was the sole author of this article.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest
M.P. is Editor-in-Chief of Current Bioscience and a member of Current Bioscience editorial board. This article was reviewed by Current Bioscience editors and reviewers. The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Lowy FD, Fant J, Higgins LL, Ogawa SK, Hatcher VB. Staphylococcus aureus-human endothelial cell interactions. J Ultrastruct Mol Struct Res [Internet]. 1988 Feb;98(2):137–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2522671. https://doi.org/10.1016/S0889-1605(88)80906-6

2. Lowe AM, Beattie DT, Deresiewicz RL. Identification of novel staphylococcal virulence genes by in vivo expression technology. Mol Microbiol [Internet]. 1998 Mar;27(5):967–76. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-2958.1998.00741.x. https://doi.org/10.1046/j.1365-2958.1998.00741.x

3. Cornelis GR. Contact with eukaryotic cells: A new signal triggering bacterial gene expression. Trends Microbiol [Internet]. 1997 Feb;5(2):43–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0966842X96300401. https://doi.org/10.1016/S0966-842X(96)30040-1

4. Zhang JP, Normark S. Induction of Gene Expression in Escherichia coli After Pilus-Mediated Adherence. Science (80-) [Internet]. 1996 Aug 30;273(5279):1234–6. Available from: https://www.sciencemag.org/lookup/doi/10.1126/science.273.5279.1234. https://doi.org/10.1126/science.273.5279.1234

5. Douthwaite AH, Trafford JAP, McGill DAF, Evans IE. Methicillin. BMJ [Internet]. 1961 Jul 1;2(5243):6–8. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.2.5243.6. https://doi.org/10.1136/bmj.2.5243.6

6. Barber M. Methicillin-resistant staphylococci. J Clin Pathol [Internet]. 1961 Jul 1;14(4):385–93. Available from: http://jcp.bmj.com/cgi/doi/10.1136/jcp.14.4.385. https://doi.org/10.1136/jcp.14.4.385

7. Boyce JM, Causey WA. Increasing Occurrence of Methicillin-Resistant Staphylococcus aureus in the United States. Infect Control [Internet]. 1982 Oct 2;3(5):377–83. Available from: https://www.cambridge.org/core/product/identifier/S0195941700057337/type/journal_article. https://doi.org/10.1017/S0195941700057337

8. Levy SB. The Challenge of Antibiotic Resistance. Sci Am [Internet]. 1998 Mar;278(3):46–53. Available from: https://www.scientificamerican.com/article/the-challenge-of-antibiotic-resista. https://doi.org/10.1038/scientificamerican0398-46

9. Kobayashi SD, Malachowa N, Whitney AR, Braughton KR,

Gardner DJ, Long D, et al. Comparative Analysis of USA300 Virulence Determinants in a Rabbit Model of Skin and Soft Tissue Infection. J Infect Dis [Internet]. 2011 Sep 15;204(6):937–41. Available from: https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/jir441. https://doi.org/10.1093/infdis/jir441

10. Jacquet R, LaBauve AE, Akoolo L, Patel S, Alqarzaee AA, Wong Fok Lung T, et al. Dual Gene Expression Analysis Identifies Factors Associated with Staphylococcus aureus Virulence in Diabetic Mice. Torres VJ, editor. Infect Immun [Internet]. 2019 Mar 4;87(5). Available from: https://iai.asm.org/content/87/5/e00163-19. https://doi.org/10.1128/IAI.00163-19

11. Malachowa N, Kobayashi SD, Sturdevant DE, Scott DP, DeLeo FR. Insights into the Staphylococcus aureus-Host Interface: Global Changes in Host and Pathogen Gene Expression in a Rabbit Skin Infection Model. Kaufmann GF, editor. PLoS One [Internet]. 2015 Feb 26;10(2):e0117713. Available from: https://dx.plos.org/10.1371/journal.pone.0117713. https://doi.org/10.1371/journal.pone.0117713

12. Cuthbertson L, Nodwell JR. The TetR Family of Regulators. Microbiol Mol Biol Rev [Internet]. 2013 Sep 1;77(3):440–75. Available from: https://mmbr.asm.org/content/77/3/440. https://doi.org/10.1128/MMBR.00018-13

13. Deochand DK, Grove A. MarR family transcription factors: dynamic variations on a common scaffold. Crit Rev Biochem Mol Biol [Internet]. 2017 Nov 2;52(6):595–613. Available from: https://www.tandfonline.com/doi/full/10.1080/10409238.2017.1344612. https://doi.org/10.1080/10409238.2017.1344612

14. Speziale P, Pietrocola G. The Multivalent Role of Fibronectin-Binding Proteins A and B (FnBPA and FnBPB) of Staphylococcus aureus in Host Infections. Front Microbiol [Internet]. 2020 Aug 26;11. Available from: https://www.frontiersin.org/article/10.3389/fmicb.2020.02054/full. https://doi.org/10.3389/fmicb.2020.02054

15. Cheung AL, Eberhardt K, Heinrichs JH. Regulation of protein A synthesis by the sar and agr loci of Staphylococcus aureus. Infect Immun [Internet]. 1997;65(6):2243–9. Available from: https://iai.asm.org/content/65/6/2243. https://doi.org/10.1128/IAI.65.6.2243-2249.1997

16. Cruz AR, Boer MA den, Strasser J, Zwarthoff SA, Beurskens FJ, de Haas CJC, et al. Staphylococcal protein A inhibits complement activation by interfering with IgG hexamer formation. Proc Natl Acad Sci [Internet]. 2021 Feb 16;118(7):e2016772118. Available from: http://www.pnas.org/lookup/doi/10.1073/pnas.2016772118. https://doi.org/10.1073/pnas.2016772118

17. Herman-Bausier P, Labate C, Towell AM, Derclaye S, Geoghegan JA, Dufrêne YF. Staphylococcus aureus clumping factor A is a force-sensitive molecular switch that activates bacterial adhesion. Proc Natl Acad Sci [Internet]. 2018 May 22;115(21):5564–9. Available from: http://www.pnas.org/lookup/doi/10.1073/pnas.1718104115. https://doi.org/10.1073/pnas.1718104115

18. Venkatasubramaniam A, Kanipakala T, Ganjbaksh N, Mehr R, Mukherjee I, Krishnan S, et al. A Critical Role for HlgA in Staphylococcus aureus Pathogenesis Revealed by A Switch in the SaeRS Two-Component Regulatory System. Toxins (Basel) [Internet]. 2018 Sep 18;10(9):377. Available from: http://www.mdpi.com/2072-6651/10/9/377. https://doi.org/10.3390/toxins10090377

19. Hodille E, Plesa A, Bourrelly E, Belmont L, Badiou C, Lina G, et al. Staphylococcal Panton–Valentine Leucocidin and Gamma Haemolysin Target and Lyse Mature Bone Marrow Leucocytes. Toxins (Basel) [Internet]. 2020 Nov 20;12(11):725. Available from: https://www.mdpi.com/2072-6651/12/11/725. https://doi.org/10.3390/toxins12110725

20. Cheng AG, McAdow M, Kim HK, Bae T, Missiakas DM, Schneewind O. Contribution of Coagulases towards Staphylococcus aureus Disease and Protective Immunity. PLoS Pathog [Internet]. 2010 Aug 5;6(8):e1001036. Available from: https://dx.plos.org/10.1371/journal.ppat.1001036. https://doi.org/10.1371/journal.ppat.1001036

21. Ko Y-P, Liang X, Smith CW, Degen JL, Höök M. Binding of Efb from Staphylococcus aureus to Fibrinogen Blocks Neutrophil Adherence. J Biol Chem [Internet]. 2011 Mar 18;286(11):9865–74. Available from: http://www.jbc.org/lookup/doi/10.1074/jbc.M110.199687. https://doi.org/10.1074/jbc.M110.199687

22. Rooijakkers SHM, Milder FJ, Bardoel BW, Ruyken M, van Strijp JAG, Gros P. Staphylococcal Complement Inhibitor: Structure and Active Sites. J Immunol [Internet]. 2007 Sep 1;179(5):2989–98. Available from: http://www.jimmunol.org/lookup/doi/10.4049/jimmunol.179.5.2989. https://doi.org/10.4049/jimmunol.179.5.2989

23. Geraci J, Neubauer S, Pöllath C, Hansen U, Rizzo F, Krafft C, et al. The Staphylococcus aureus extracellular matrix protein (Emp) has a fibrous structure and binds to different extracellular matrices. Sci Rep [Internet]. 2017 Dec 20;7(1):13665. Available from: http://www.nature.com/articles/s41598-017-14168-4. https://doi.org/10.1038/s41598-017-14168-4

24. Johnson M, Cockayne A, Morrissey JA. Iron-Regulated Biofilm Formation in Staphylococcus aureus Newman Requires ica and the Secreted Protein Emp. Infect Immun [Internet]. 2008 Apr;76(4):1756–65. Available from: https://iai.asm.org/content/76/4/1756. https://doi.org/10.1128/IAI.01635-07

25. Zhu Q, Liu B, Sun B. SpoVG Modulates Cell Aggregation in Staphylococcus aureus by Regulating sasC Expression and Extracellular DNA Release. Ercolini D, editor. Appl Environ Microbiol [Internet]. 2020 May 22;86(15). Available from: https://aem.asm.org/content/86/15/e00591-20. https://doi.org/10.1128/AEM.00591-20

26. Bestebroer J, Poppelier MJJG, Ulfman LH, Lenting PJ, Denis C V., van Kessel KPM, et al. Staphylococcal superantigen-like 5 binds PSGL-1 and inhibits P-selectin–mediated neutrophil rolling. Blood [Internet]. 2007 Apr 1;109(7):2936–43. Available from: https://ashpublications.org/blood/article/109/7/2936/125647/Staphylococcal-superantigenlike-5-binds-PSGL1-and. https://doi.org/10.1182/blood-2006-06-015461

27. Langley R, Wines B, Willoughby N, Basu I, Proft T, Fraser JD. The Staphylococcal Superantigen-Like Protein 7 Binds IgA and Complement C5 and Inhibits IgA-FcαRI Binding and Serum Killing of Bacteria. J Immunol [Internet]. 2005 Mar 1;174(5):2926–33. Available from: http://www.jimmunol.org/lookup/doi/10.4049/jimmunol.174.5.2926. https://doi.org/10.4049/jimmunol.174.5.2926

28. Smit J, Søgaard M, Schønheyder HC, Nielsen H, Frøslev T, Thomsen RW. Diabetes and risk of community-acquired Staphylococcus aureus bacteremia: a population-based case–control study. Eur J Endocrinol [Internet]. 2016 May;174(5):631–9. Available from: https://eje.bioscientifica.com/view/journals/eje/174/5/631.xml. https://doi.org/10.1530/EJE-16-0023

29. Lee Y. Targeting virulence for antimicrobial chemotherapy. Curr Opin Pharmacol [Internet]. 2003 Oct;3(5):513–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1471489203001176. https://doi.org/10.1016/j.coph.2003.04.001

30. Cohen P, Bouaboula M, Bellis M, Baron V, Jbilo O, Poinot-Chazel C, et al. Monitoring Cellular Responses to Listeria monocytogenes with Oligonucleotide Arrays. J Biol Chem [Internet]. 2000 Apr;275(15):11181–90. Available from: https://linkinghub.elsevier.com/retrieve/pii/S002192581980964X. https://doi.org/10.1074/jbc.275.15.11181

31. Rosenberger CM, Scott MG, Gold MR, Hancock REW, Finlay BB. Salmonella typhimurium Infection and Lipopolysaccharide Stimulation Induce Similar Changes in Macrophage Gene Expression. J Immunol [Internet]. 2000 Jun 1;164(11):5894–904. Available from: http://www.jimmunol.org/lookup/doi/10.4049/jimmunol.164.11.5894. https://doi.org/10.4049/jimmunol.164.11.5894

32. Ichikawa JK, Norris A, Bangera MG, Geiss GK, van 't Wout AB, Bumgarner RE, et al. Interaction of Pseudomonas aeruginosa with epithelial cells: Identification of differentially regulated genes by expression microarray analysis of human cDNAs. Proc Natl Acad Sci [Internet]. 2000 Aug 15;97(17):9659–64. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.160140297. https://doi.org/10.1073/pnas.160140297

33. DiMango E, Ratner AJ, Bryan R, Tabibi S, Prince A. Activation of NF-kappaB by adherent Pseudomonas aeruginosa in normal and cystic fibrosis respiratory epithelial cells. J Clin Invest [Internet]. 1998 Jun 1;101(11):2598–605. Available from: http://www.jci.org/articles/view/2865. https://doi.org/10.1172/JCI2865